EXHIBIT 10

Reexam

Patent
Attorney's Docket No. 22338-10230

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Control Nos.:	**90/007,542** **90/007,859**		Group Art Unit:	3991
Confirmation Nos.:	7585 ('542) 6447 ('859)		Examiner:	B.M. Celsa
Filed:	13 May 2005 23 December 2005	('542) ('859)		
Patent Owner:	Genentech, Inc. and City of Hope			

For: Merged Reexaminations of U.S. Patent No. 6,331,415 (Cabilly *et al.*)

RESPONSE UNDER 37 C.F.R. § 1.550(b)

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COMMISSIONER FOR PATENTS
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Sir:

This communication timely responds to the final Office action mailed on February 25, 2008. By petition granted on March 19, 2008, the original response date of April 25, 2008 was extended until June 6, 2008.

Patent Owners ("Owners") respectfully request reconsideration of the claims in view of the following remarks.

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REMARKS

I. Preliminary Matters

A. Information Disclosure Statement

Owners thank the Office for the indication that all materials previously submitted to the Office have been fully considered. Owners respectfully request consideration of materials provided in the accompanying supplemental information disclosure statement.

B. Interview Summary

Owners thank Examiners Celsa, Jones and Padmashri for the courtesy of an interview held on April 2, 2008. Owners' summary of the interview is provided in Attachment A to this response, in compliance with 37 C.F.R. § 1.560(b).

C. Status of Litigation Involving the '415 Patent

Owners have previously indicated that U.S. Patent No. 6,331,415 ("the '415 patent") has been the subject of litigation in the Central District of California. Owners now report that the parties to that litigation have jointly requested dismissal of the action with prejudice pursuant to a settlement agreement between the parties, and that the dismissal was ordered on June 4, 2008. Owners also report that on May 30, 2008, an action was filed in the Central District of California by Centocor seeking, inter alia, a declaratory judgment that the '415 patent is invalid and not enforceable. A copy of the complaint is provided in the accompanying information disclosure statement.

D. Additional Evidence Provided with this Response

Owners submit and request favorable consideration of this response and the accompanying declarations under 37 C.F.R. § 1.132 of Dr. Steven McKnight and Dr. Finton Walton. Owners submit the declaration of Dr. McKnight in response to new scientific findings of the Office in the final Office action ("Final Action"). Owners submit the declaration of Dr. Walton in response to the Office's observations about the legal significance of licensing of Axel (U.S. Patent No. 4,399,216), and in support of the non-obviousness of the '415 patent claims.

Owners submit that "good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented" exist pursuant to 37 C.F.R. § 1.116. Specifically, the

Office makes new factual determinations, and advances new or changed theories to support rejections in the Final Action, particularly at pages 21-46. Examples include: use of Moore (U.S. Patent No. 5,840,545) to support findings of obviousness of co-expression despite a significantly changed interpretation of the Moore prior art disclosure (Final Action at 5, 15-16); reliance on Axel as teaching production of "functional proteins" (Final Action at 30); reliance on Ochi (Ochi et al., Nature 302: 340-42 (1983)) and Oi (Oi et al., Proc. Nat'l. Acad. Sci. (USA) 80: 825-29 (1983)) as providing additional motivation to co-transform host cells (Final Action at 38); use of Dallas (PCT Publication No. WO 82/03088) to modify the teachings in Moore (Final Action at 40); and references to licensing of Axel (Final Action at 46). Owners could not have reasonably predicted that the Office would make these new or changed findings, or use them to support the rejections set forth in the Final Action. The declarations of Drs. McKnight and Walton respond to these new issues. Owners submit that presentation of the present declaration evidence is thus appropriate under 37 C.F.R. § 1.116.

II. Response to Rejections

A. Withdrawn Rejections

Owners appreciate withdrawal of rejections under 35 U.S.C. §§ 102 and 103, and for double patenting, based on Moore, alone or in combination with the '567 patent (U.S. Patent No. 4,816,567), Axel and Accolla (Accolla et al., Proc. Nat'l. Acad. Sci. (USA) 77(1): 563-66 (1980)). The Office indicates that Moore is entitled to a § 102(e) effective date for "*single host expression* of variable light and heavy chain for producing single-chain antibody" only as of "the June 5, 1995 date since the original 06/358,414 specification and claims 1-25 only disclose the separate expression of the heavy and light chain antibody fragment in different host cells . . . ." Final Action at 5 (emphasis original). The Office also indicates that Moore does not have support for "single host expression of variable light and heavy chains . . ." prior to June 5, 1995.[1] Id. at 6.

[1] At page 16 of the Final Action, the Office states that Moore "discloses a method of making 'an immunologically functional fragment' comprising independently expressing in a host cell variable and heavy light chain domains . . . ." This appears to be an inadvertent error in view of the Office's conclusions noted above.

B. Summary of the Rejections

The Office rejects claims 1-36 for obviousness-type double patenting based on the '567 patent, in view of Axel, Rice (Rice et al., Proc. Nat'l. Acad. Sci. (USA) 79: 7862 (1982)) and Kaplan (European Patent No. 0044722), further in view of Dallas, and further in view of Deacon (Deacon et al., Biochem. Soc. Trans. 4: 818-20 (1976)), Valle 1981 (Valle et al., Nature 291: 338-40 (1981)), or Ochi, alone or further in view of Moore. Dependent claims 10 and 27-32 are rejected when these references are further considered with Builder (U.S. Patent No. 4,511,502), and dependent claim 22 is further rejected in view of Accolla. The Office sets forth the basis of its rejections at pages 10 to 20 of the Final Action. At pages 21 to 46, the Office addresses issues raised by Owners in their previous responses.

The Office bases the final rejection on two conclusions, namely: (i) "One of ordinary skill in the art would have been motivated to express, in a single host, light and heavy immunoglobulin chains (using one or two vectors) when viewing the reference Cabilly 1 ['567] patented invention in light of the prior art" (Final Action at 12); and (ii) "The prior art provides further motivation to make active antibody with a reasonable expectation of success" (Final Action at 14). Owners respectfully request withdrawal of the rejections because the Office's conclusions are inconsistent with the collective teachings and suggestions of the cited references, and with the beliefs and expectations of the person of ordinary skill in the art in early April 1983.

Owners respectfully traverse the rejections set forth in the Final Action, and request withdrawal of rejections of claims 1-36.

C. Brief Summary of Why the '415 Claims Are Not Obvious From the '567 Claims and in View of the Prior Art

Owners provide with this response a second declaration by Dr. Steven McKnight responding to issues raised in the Final Action. Dr. McKnight accurately presents the views of a person of ordinary skill in the art in April 1983, based on his relevant experience and training from that time. He explains that, unlike the '567 claims, the '415 patent claims require three separate steps: (i) a host cell must be transformed with immunoglobulin heavy chain and light chain DNA sequences; (ii) the DNA sequences must be independently expressed (transcribed and translated) by the host cell to produce polypeptides; and (iii) the polypeptides must be

assembled to form an immunoglobulin molecule or an immunologically functional immunoglobulin fragment ("fragment"). See McKnight 2nd Dec. ¶¶ 4-5.

The inventions of the '415 and '567 patents have distinct utilities and applications linked to the distinct methods and results each patent requires. For example, the common specification of the patents identifies distinct benefits of producing immunoglobulin molecules and fragments using individually produced chains, relative to the benefits of making such molecules or fragments by expressing both chains in one host cell pursuant to the '415 patented methods. See, e.g., '415 patent, col. 14, lns. 20-49; col. 12, lns. 50-56. The evidence also establishes that the products made by each patented method are distinct, and have independent benefits and applications. See, e.g., McKnight 2nd Dec. ¶ 15; Riggs Dec. ¶¶ 19-29.

The evidence of record demonstrates that the material distinctions between the '415 and '567 patent claims would not have been obvious to a person of ordinary skill in the art in April 1983. In particular, this evidence establishes that:

- the cited references do not suggest expressing heavy and light chain polypeptides in a single transformed host cell, but instead teach away from doing this;
- a person of ordinary skill would not have believed that what was required by the '415 patent claims could have been predictably achieved in April 1983 based on the '567 claims, and from what is disclosed in the cited references and generally known in the field at that time; and
- secondary considerations support the non-obviousness of the '415 claims.

These findings establish that the '415 claims would not have been considered obvious in April 1983 based on the '567 claims in view of the cited art.

1. The Cited Art Teaches Away from Expression of Heavy and Light Chain Polypeptides in a Single Transformed Host Cell

Dr. McKnight explains that the cited references reflect the prevailing mind-set in April 1983 that only one eukaryotic polypeptide of interest should be produced in a recombinant host cell. See McKnight 2nd Dec. ¶¶ 7-9. As he explains, the cited references all show the unpredictability of successfully expressing and recovering even one eukaryotic polypeptide from a host cell in April 1983. See id. at ¶¶ 8, 21-23, 30-34. He also explains that the prevailing mindset would have led a person of ordinary skill to break down a complex project, such as

production of a multimeric eukaryotic protein, into more manageable steps (e.g., produce each constituent polypeptide of the multimer in a separate host cell, as was proposed in Moore and Kaplan). See id. at ¶¶ 7-13.

Dr. McKnight explains that this mindset is reflected in Axel. He explains that a person of ordinary skill in the art would have necessarily read the Axel DNA I + DNA II scheme as suggesting production of only a single antibody polypeptide at a time in a co-transformed host. See id. at. ¶¶ 19, 27. Moreover, as he explains, while Axel shows successful cotransformation with a "DNA I" (e.g., a β-globin gene) and a "DNA II" (a marker gene such as thymidine kinase), it shows unsuccessful coexpression of both sequences. See id. at ¶¶ 20-22. Specifically, Axel reports incorrect transcription of the DNA I sequence and no production or recovery of the polypeptide encoded by it. See id. at ¶ 21. Axel thus does not show production of two "functional" polypeptides in a co-transformed cell.

The Axel prosecution history clearly supports Dr. McKnight's analysis. In particular, the Axel inventors conceded that the disclosure in their patent did not describe production and recovery of functional proteins encoded by a DNA I sequence, and eventually accepted claims that deleted any reference to expression of a protein encoded by a "DNA I." See Application Serial No. 06/124,513; Paper No. 9, dated February 8, 1982 at p. 2, ¶ 12; Paper No. 15, dated January 12, 1983 at pp. 2-3, 6; and Paper No. 17, dated February 7, 1983.

Dr. McKnight explains that Rice, Ochi, and Oi reinforce the unpredictability shown in Axel. See McKnight 2nd Dec. ¶¶ 30-34. He points out that the three references describe experiments where lymphoid cells were transformed with, and expressed, only a single foreign immunoglobulin light chain gene. He explains how a person of skill would have interpreted the experimental results reported in these papers, and, in particular, why such a person would have found them to be reporting substantial unpredictability. See, e.g., id. at ¶¶ 31-34; He also explains why none of the publications describes or suggests expressing two different foreign immunoglobulin genes in a single transformed host cell. See id. at ¶¶ 5, 34.

Dr. McKnight also discusses Moore and Kaplan, and demonstrates that these references actually teach away producing immunoglobulins and fragments in a single host cell according to the approach of the '415 patent. He explains that, instead, each reference expressly describes a

plan for producing an immunoglobulin molecule or fragment using heavy and light chain polypeptides that have been produced in separate host cells. See id. at ¶¶ 12, 13.

Dr. McKnight then explains why Dallas does not suggest modifying the '567 claims or the teachings of other cited art to yield the '415 claimed invention. See id. at ¶¶ 38-48. He explains that Dallas describes experiments where E. coli genes encoding simple E. coli cell surface proteins are used to transform an E. coli host cell. See id. at ¶¶ 39-41. He explains that a person of ordinary skill would have evaluated Dallas in conjunction with what is reported in the other cited references, in particular, the unpredictability reported in Axel, Rice, Ochi and Oi, and the express teachings of Kaplan and Moore to express heavy and light chains polypeptides in separate host cells. See id. at ¶¶ 38-39, 47-48. He also explains why the Dallas E. coli teachings would not be considered relevant to production of multimeric eukaryotic proteins. See id. at ¶¶ 42-47. Indeed, Owners note that during examination of the U.S. counterpart to Dallas, the Office limited the Dallas claims to the specific transformed E. coli host cells and E. coli genes described in the Dallas examples.[2] As Dr. McKnight concludes after reading Dallas with the teachings of the other references, "a person of ordinary skill would have simply avoided all these problems and uncertainties by producing the heavy and light immunoglobulin chains in separate bacterial host cell cultures." Id. at ¶ 48.

2. A Person of Ordinary Skill Would Not Have Viewed the Cited References as Making Achievement of the '415 Inventions Predictable

A person of ordinary skill in the art would not have had a reasonable basis for believing the '415 patented invention as a whole could have been predictably achieved based on the '567 patent claims, when considered with the teachings of the cited references and the general knowledge in the art.

As Dr. McKnight explains, Axel, Rice, Ochi, and Oi each report experimental results that cumulatively show significant unpredictability in achieving successful expression of one recombinant DNA sequence encoding one foreign polypeptide. Axel reports experimental results showing only unsuccessful efforts to express a single DNA I sequence in a co-

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[2] See file wrapper of U.S. Patent No. 5,137,721 (e.g., Office action of October 28, 1982 (Paper No. 4) at 4; Office action of June 5, 1984 (Paper No. 11) at 3-4; Office action of November 17, 1986 (Paper No. 17) at 3).

transformed eukaryotic host cell. See McKnight 2nd Dec. ¶¶ 21-22. Similarly, Rice, Ochi, and Oi report significant unpredictability in achieving successful expression of a single light chain immunoglobulin gene in various types of lymphoid cells.[3] McKnight 2nd Dec. ¶¶ 30-34. These reports of inconsistent and unpredictable experimental results would not have led a person of ordinary skill to believe that independent expression of DNA sequences encoding heavy and light immunoglobulin chain polypeptides in one transformed host cell – a substantially more complex undertaking – could have been predictably achieved in April 1983. See, e.g., See id. at ¶¶ 5-8, 50.[4]

Neither Moore nor Kaplan would have changed the expectations of the person of ordinary skill when considered with the other references. Neither includes experimental results that would counter what Axel, Rice, Ochi and Oi show, and each specifically directs the person of ordinary skill to produce heavy and light chain polypeptides in separate host cell cultures. See, e.g., McKnight 2nd Dec. ¶¶ 12-16.[5] Similarly, Dallas would not have altered the expectations of a person of ordinary skill in the art attempting to achieve the '415 patented invention because of a person of ordinary skill would not find that its teachings would answer questions raised by the other publications or provide guidance relevant to production of eukaryotic proteins. See, e.g., McKnight 2nd Dec. ¶¶ 39-40, 42-47; McKnight 1st Dec. ¶¶ 99-101; Harris 2nd Dec. ¶¶ 72-76; Botchan Dec. ¶¶ 79-82. Moreover, Dallas reports unpredictable results in far simpler experiments involving E. coli gene expression. See, e.g., McKnight 2nd Dec. ¶ 41; Harris 2nd Dec. ¶ 77.

Deacon and Valle 1981 also would not have changed the reasonable expectations of a person of ordinary skill in April 1983 about predictably achieving the '415 invention as a whole. These references do not describe experiments that involve successful transformation, correct transcription of foreign DNA, and successful translation of mRNA in the transformed host cells.

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[3] Moreover, as Dr. Rice explained, using the techniques described in the Rice paper, he attempted to introduce and express single immunoglobulin genes into lymphoid cell lines other than those described in the Rice paper, and in most of the experiments he could not produce stable transfectants. See Rice 1st Dec. ¶ 14.

[4] See also Harris 1st Dec. ¶¶ 22-28, 57-59, 62-63, 80-86; Botchan Dec. ¶¶ 63-66, 97-103.

[5] See also McKnight 1st Dec. ¶¶ 14-18, 26-39, 92-96; Harris 2nd Dec. ¶¶ 68-70; Botchan Dec. ¶¶ 38, 75-77; Altman Dec. ¶ 15

See, e.g., McKnight 2nd Dec. ¶¶ 51-54; Harris 2nd Dec. ¶¶ 91-97; Botchan Dec. ¶¶ 86-94; Colman Dec. ¶¶ 15, 30, 32, 36.

3. There is Substantial Evidence of Secondary Indicia of Non-Obviousness of the '415 Claimed Inventions

As Dr. Walton explains, the '415 patent has been extensively licensed to third parties for production of antibodies according to its claimed methods, including companies that have also licensed the Axel patent. He analyzes and explains the significance of the substantial royalty payments for these licenses. He observes that payments made under '415 licenses are independent of payments made for licenses under the '567 patent. Walton Dec. ¶¶ 25-27. The licensing of the '415 patent by many sophisticated biotechnology and pharmaceutical companies shows recognition of the merits of the '415 patent claims independent of the '567 patent claims. Id. The royalty payments made by licensees attributable only to the '415 patent over many years also show commercial success of the '415 patented inventions, and that this is independent of the commercial success of the '567 patent. Walton Dec. ¶¶ 34-37, 44-46.

D. Detailed Response to the Rejections

Obviousness-type double patenting analyses are made using the same obviousness framework required by 35 U.S.C. § 103, except that the claim of the earlier patent is used as the reference point and not as prior art. See, e.g., M.P.E.P. § 804(II)(B)(1).[6] Obviousness determinations, in turn, are made on the basis of factual determinations pursuant to Graham v. John Deere Co., 383 U.S. 1, 148 U.S.P.Q. 459 (1966).[7] See KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734, 82 U.S.P.Q.2d 1385, 1391 (2007) ("If a court, or patent examiner, conducts this [Graham] analysis and concludes the claimed subject matter was obvious, the claim is invalid under § 103.").

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[6] See also General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1281, 23 U.S.P.Q.2d 1839, 1846 (Fed. Cir. 1992); In re Longi, 759 F.2d 887, 892, 225 U.S.P.Q. 645, 648 (Fed. Cir. 1985).

[7] The distinctions between the claims, the teachings of the prior art, the level of ordinary skill in the art, and secondary evidence of non-obviousness are all required factual determinations. See Studiengesellschaft Kohle mbH v. Northern Petrochemical Co., 784 F.2d 351, 355, 228 U.S.P.Q. 837, 840 (Fed. Cir. 1986).

In KSR, the Court emphasized the important role that predictability in the field of the invention plays in an obviousness determination.[8] One must consider whether uncertainty or unpredictability in the field of the invention would have led a person of ordinary skill in the art to conclude that a proposed invention was not obvious, even if there is some general suggestion or desire to attempt to produce the invention. KSR, 127 S.Ct. at 1731, 82 U.S.P.Q.2d at 1396 ("a court must ask whether the improvement is more than the predictable use of prior art elements"); See also M.P.E.P. § 2145(X)(B); In re Vaeck, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991). And where the path taken by the patent owner was contrary to what was suggested in the prior art (e.g., because it was believed the patented result could not be predictably achieved), that prior art can be said to teach away from the invention. Where this occurs, the invention is less likely to be obvious. See KSR, 127 S.Ct. at 1739-40, 82 U.S.P.Q.2d at 1395 (noting the principle that "when the prior art teaches away from a combination, that combination is more likely to be nonobvious").

Indeed, it is well settled law that "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re ICON Health and Fitness, Inc., 496 F.3d 1374, 1381; 83 U.S.P.Q.2d 1746, 1751 (Fed. Cir. 2007) (quoting In re Gurley, 27 F.3d 551, 553; 31 U.S.P.Q.2d 1130, 1131 (Fed.Cir. 1994)). (emphasis added) See also Takeda Chem. Indus. v. Alphapharm Pty, Ltd., 492 F.3d 1350, 1358-1359, 83 U.S.P.Q.2d 1169, 1175-76 (Fed. Cir. 2007) (affirming the district court's finding of nonobviousness based, in part, on a finding that the prior art taught away from the compound selected by patentee); In re Omeprazole Patent Litigation, 490 F. Supp. 2d 381, 531 (S.D.N.Y. 2007) (finding nonobviousness, in part based on conclusion that "[b]ecause the goals of these [prior art] patents and the claimed inventions diverge, they teach away . . . ."). Owners submit that this is precisely what is shown by the cited references and the evidence of record in this case.

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[8] Predictability in the result of assembling "known" components was a critical factor in KSR. See, e.g., KSR, 127 S.Ct. at 1742; 82 U.S.P.Q.2d at 1397 ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." (emphasis added)). Central to the KSR holding was the determination that there was no doubt that the combination would work as expected, and that nothing taught away from the combination. KSR, 127 S.Ct. at 1744, 82 U.S.P.Q.2d at 1399.

As explained below, the substantial evidence of record establishes that:

(i) the teachings of the cited references collectively teach away from the '415 claimed inventions because they direct the person of ordinary skill to not produce more than one immunoglobulin polypeptide at a time in a recombinant host cell;

(ii) a person of ordinary skill would not have believed recombinant production of two different immunoglobulin polypeptides in a single transformed host cell could have been predictably achieved in April 1983 based on the methodologies and results described in the cited references and the general knowledge and experience that person would have had at that time; and

(iii) substantial evidence of secondary indicia of nonobviousness exists for the '415 patent claims.

As a result, a person of ordinary skill in the art would not have considered the '415 claims to have been obvious over the '567 claims in conjunction with the cited references.

1. The '567 Patent Claims Do Not Suggest Producing Heavy and Light Chains in One Transformed Host Cell

The claims of the "reference" patent are the starting point of an obviousness-type double patenting analysis. In this case, the '567 claims require production of only one chimeric heavy or light chain polypeptide in a transformed host cell. The '415 patent, by contrast, requires production of an immunoglobulin molecule or fragment by a process in which DNA sequences encoding both the heavy and light chain polypeptides are independently expressed in one host cell. See, e.g., McKnight 2nd Dec. ¶¶ 7, 17-34 ; Harris 2nd Dec. ¶¶ 21-33; Botchan Dec. ¶¶ 62, 67, 69-72; see also infra §§ II(C), II(D)(4).

The common disclosure of the '415 and '567 patents expressly states that producing individual chains is one of the objectives of the invention.[9] It also explicitly identifies benefits of producing individual chains in separate host cells. For example, the disclosure indicates that "[t]he ability of the method of the invention to produce heavy and light chains or portions thereof, in isolation from each other offers the opportunity to obtain unique and unprecedented assemblies of immunoglobulins, Fab regions, and univalent antibodies."[10] And, as Dr. Riggs

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[9] See '567 patent at col. 5, lns. 32-36.

[10] See id. at col. 13, lns. 28-32; see also, e.g., id. at col. 15, lns. 44-57 (describing hybrid antibodies); and id. at col. 16, lns. 33-54 (describing univalent antibodies).

previously explained, individual chains produced pursuant to the '567 claims have practical utilities independent of their use in producing immunoglobulin molecules or fragments.[11] The Office has presented no contrary evidence to rebut any of these points.

Nonetheless, the Office concludes that "the Cabilly 1 claims encompass making of an antibody as the most preferred utility"[12] because these claims "teach the recombinant method of making light and heavy chains which would motivate one of ordinary skill in the art to make an antibody or antibody fragment."[13] The Office overlooks a fundamental point – the potential use of individually produced chimeric heavy or light chains to produce an immunoglobulin molecule or fragment does not inherently or explicitly suggest that one should produce both chains in one transformed host cell. The common patent disclosure clearly explains that these are two distinct approaches of producing antibody molecules and fragments,[14] with each providing particular and independent benefits.[15]

In fact, producing an immunoglobulin by assembling individually produced heavy and light chains after the chains have been isolated from the host cell necessarily precludes use of the '415 patented methods – considered as a whole as they must – for making these molecules or fragments. This is because after the chains have been individually produced in separate cell cultures, they cannot be "produced" together in the same host cell. Taking the next (and unclaimed) step of assembling an immunoglobulin molecule or fragment after the chains simply have been produced by the '567 methods simply does not implicate the '415 patented method of making these molecules or fragments by expressing both polypeptides in one host cell.

The two distinct approaches thus are not scientifically or legally equivalent. Scientifically, there is no question that the technical challenges in, and predictability of,

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[11] See Riggs Dec. ¶¶ 19-32; November 2005 response at pp. 18-20.

[12] Final Action at 25.

[13] Final Action at 23. Owners again submit using the '567 disclosure or claims as a "teaching" or source of "motivation" is improper. See, e.g., May 2007 Response at 30-35, In re Vogel, 422 F.2d 438, 441, 164 U.S.P.Q. 619, 622 (C.C.P.A. 1970); General Foods Corp., 972 F.2d at 1281, 23 U.S.P.Q.2d at 1846 (patent claim not to be used as prior art); In re Aldrich, 398 F.2d 855, 859, 158 U.S.P.Q. 311, 316 (C.C.P.A. 1968).

[14] See, e.g., '567 patent at col. 12, lns. 58-65.

producing two different eukaryotic proteins and assembling them into a multimeric protein structure in April 1983 were not equivalent to the challenges and predictability of producing only one eukaryotic protein in a transformed host cell. See infra § II(D)(3); see, e.g., McKnight 2nd Dec. ¶¶ 7, 17-34; Harris 2nd Dec. ¶¶ 21-33; Botchan Dec. ¶¶ 62, 67, 69-72. Legally, they are also distinct (e.g., the '415 patent requires production of an immunoglobulin molecule or fragment, while the '567 patent requires production of only a heavy or a light chimeric chain).[16]

The Office cites Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC, 329 F.3d 1373, 68 U.S.P.Q.2d 1865 (Fed. Cir. 2003), to justify its use of the common disclosure to find a utility of the '567 patent claims that might suggest the later patented '415 invention. See Final Action at 24. In particular, the Office notes that "consideration of the underlying specification by the CAFC revealed the disclosure of only a single utility which was subsequently claimed in the second patent." Final Action at 23-24.

Geneva Pharmaceuticals is not applicable to the facts of this case. In Geneva, the first patent claimed a product and the second patent claimed the only use of that product. Here, the '567 and '415 patents define materially distinct methods, each having distinct uses and applications, and each requiring materially distinct results. Moreover, making immunoglobulin molecules or fragments using the individually produced chimeric chains according to the '567 patent offers distinct benefits and advantages relative to making these molecules or fragments by the processes of '415 patent claims. Also, uncontested evidence shows that the individual chains have practical utility independent of using them to produce immunoglobulin molecules or fragments. See Riggs Dec. ¶¶ 19-32. Thus, unlike in Geneva, the '567 patent claims do not require producing a "product" having a single use that is claimed by the '415 patent. In fact, using individually produced chains to produce an immunoglobulin molecule or fragment

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[15] The common patent disclosure plainly identifies distinct benefits of each pathway. See, e.g., id. at col. 13, lns. 28-32; col. 13, lns. 19-21 ("When heavy and light chain are coexpressed in the same host, the isolation procedure is designed so as to recover reconstituted antibody.").

[16] Owners have previously catalogued numerous instances during the examination of the '567 and '415 patents where the Office found patentable distinctions to exist between claims requiring production of heavy and light chains and claims requiring production of only one immunoglobulin polypeptide. See Nov. 2005 Response at 10-11; Oct. 2006 Response at 6-7; Lee Dec. ¶¶ 4, 10-12, 17-18, 20. These past determinations support finding the '415 claims patentably distinct over the '567 claims.

necessarily precludes one from using the '415 patented process requiring production of both chains in one host cell to make such molecules or fragments.

The common patent disclosure reinforces these patentable distinctions by identifying independent benefits of the two ways of producing immunoglobulin molecules and fragments, and by identifying distinct practical applications for individually produced immunoglobulin chains (i.e., other than to produce immunoglobulin molecules or fragments). See McKnight 2nd Dec. ¶ 15 and Riggs Dec. ¶¶ 19-32. Accordingly, the fact that individually produced '567 immunoglobulin chains might be used to produce immunoglobulin molecules or fragments is legally irrelevant to the question of double patenting under the rationale of Geneva Pharmaceuticals.

2. Co-Transformation of Host Cells with Two DNA Sequences Is Not Equivalent to Co-Expression of Those Sequences

The Office relies on two key observations about Axel. First, it reads Axel as teaching successful co-expression of two different DNA sequences based on its conclusion that "co-transformation is synonymous with coexpression." Final Action at 29. Second, it reads Axel as teaching production of two "functional" proteins in a co-transformed host cell. See Final Action at 28-29 ("The Axel patent clearly possesses the concept of co-transforming a single eukaryotic or mammalian host cell to express functional proteins."). The Office relies on these findings to conclude that Axel specifically suggests "expressing two immunoglobulin chains in a single eukaryotic host cell, since *Axel* discloses and claims encoding an antibody that necessarily possesses both light and heavy immunoglobulin chains." Final Action at 30.

As Dr. McKnight explains, Axel itself shows that the steps of transformation and expression clearly are not synonymous or scientifically equivalent. See McKnight 2nd Dec. ¶¶ 17-23. In addition, Axel reports no production or recovery of any "functional" proteins other than the marker protein that changed the phenotype of the transformed host cells, which is reinforced by the Axel prosecution history. See id. at ¶ 21. As a consequence, Axel does not specifically suggest expressing heavy and light immunoglobulin chains in a single transformed host cell. See id. at ¶¶ 24-29.

(a) The Axel Patent Shows that Co-Transformation Was Not Equivalent to Co-expression

Axel reports two series of experiments in which the inventors tried to express a "DNA I" sequence. In each, one DNA I sequence was used to co-transform a eukaryotic host cell along with a "marker" gene (DNA II). See McKnight 2nd Dec. ¶¶ 18-20. Axel reports that the host cells were successfully co-transformed with the two different DNA sequences. See id. at ¶¶ 17-18, 21. This report is based on experiments that show that both of the DNA I and DNA II sequences were found in progeny of the cells that were subjected to the transformation process. See id. at ¶ 21.

In both series of experiments, Axel reports that only the marker gene (DNA II) was successfully expressed. See id. at ¶¶ 20-22. In other words, Axel reports that no DNA I sequence was successfully expressed by host cells co-transformed with that sequence and a DNA II (marker gene) sequence. See id. at ¶¶ 21-22. Instead, Axel reports abnormal transcription of the DNA I sequence in the only experiment where this was evaluated (i.e., where DNA I encoded the rabbit ß-globin polypeptide).[17] See id. at ¶¶ 22-23. And Axel reports that no rabbit ß-globin protein was detected in, or recovered from, the co-transformed cells. See id. at ¶ 21.

These experimental results reported in Axel demonstrate that the steps of transformation and expression are not synonymous. See id. at ¶ 23. A person of ordinary skill in the art, accordingly, would not have read Axel as showing or suggesting that one could predictably achieve co-expression of two different DNA sequences in a single host cell simply by demonstrating that the cell had been successfully "co-transformed" with these two sequences. See id. at ¶¶ 23, 26.

(b) The Axel Patent and its Prosecution History Show No Production or Recovery of "DNA I Polypeptides"

Axel also does not describe successful production or recovery of any "functional" proteins encoded by a DNA I sequence. As Dr. McKnight points out, Axel refers only to

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[17] The Axel showing of incorrect transcription also illustrates why a person of ordinary skill would not have equated the expression of foreign DNA with translation of mRNA fractions injected into a Xenopus oocyte in that experimental model system. See Final Action at 41 (suggesting that the teachings of Deacon and Valle 1981 "do not depend on the genetic material used, since once expressed, the ability of the two chains to assemble into an immunoglobulin does not depend on the genetic material used for such expression").

production of "functional" protein encoded by the marker gene (DNA II) that transformed the phenotype of the cell. [18] See McKnight 2nd Dec. ¶¶ 20-21. Indeed, Axel itself clearly shows that no protein encoded by a DNA I sequence was detected in or recovered from a co-transformed host cell in the experiments that were described in the Axel specification. See id. at ¶¶ 21-23. Because Axel does not show or suggest production or recovery of two "functional" foreign proteins in a cotransformed host cell, there is no scientific basis for the proposition that Axel specifically suggests production of a "functional antibody" by expressing two different foreign DNA sequences encoding heavy and light antibody chains in one transformed host cell.

This reading of the Axel disclosure is the only one that is consistent with the prosecution history of Axel, which shows that the Axel applicants' canceled claims "directed to the production of protein from DNA I" in the face of repeated enablement rejections by the Office. For example, during examination of the application that matured into the '216 patent, the examiner rejected certain original claims under § 112, first paragraph, as "based on a specification which is non-enabling in regard to producing protein products." Axel Office Action dated July 14, 1981 at ¶ 8. The examiner stated "although the globin gene is inserted, no protein is recovered." Id.[19]

The Axel applicants eventually canceled the rejected claims in an after-final amendment filed on January 12, 1983 (Paper No. 15). The canceled claims had been rejected "based upon the lack of actual working examples of foreign protein production by cotransformed cells." Id. at 3. The Axel applicants clearly stated that claims "directed to the production of proteins from DNA I" were being canceled. See January 12, 1983 Reply; see also id. at 6 (applicants "canceled claims directed to production of protein from DNA I" "in a sincere effort to place [the] application in condition for allowance"). And, when the examiner finally allowed the claims issued in the '216 patent, she revised the abstract to delete all references to production of

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[18] Under the Axel scheme, the DNA I sequence encodes the polypeptide that one hopes to produce and recover from the cell – the DNA II encodes the selectable marker transforms the phenotype of the cell to enable use of selective pressure. See, e.g., McKnight 2nd Dec. ¶¶ 18-19; Botchan Dec. ¶¶ 48, 50; Harris 1st Dec. ¶¶ 21-24; Harris 2nd Dec. ¶ 38; McKnight 1st Dec. ¶¶ 66, 74.

[19] See also Axel Office action mailed February 8, 1982 at ¶ 12, where, in response to Axel's assertion that production of functional thymidine kinase protein was sufficient, the examiner found that the rejected claims specifically required "recovery of the protein from DNA I ... [which is] not shown" (emphasis added). Id.

"proteinaceous materials" including in particular the laundry list of examples that includes "antibodies." See July 5, 1983 Examiner's Amendment (Paper No. 18).[20]

Thus, based on its disclosure and prosecution history, Axel plainly does not show that production or recovery of even one "functional" polypeptide encoded by a DNA I sequence was routine or predictable. There is no legitimate scientific or legal basis for finding that the Axel description suggested that production of two different antibody polypeptides (in addition to a "functional" selectable marker protein) in a single transformed host cell would have been routine or could have been predictably achieved based on its teachings.

Owners note that Dr. Axel provided a declaration under 37 C.F.R. § 1.132 in a related Cabilly application (08/422,187) in which he, like Dr. McKnight, characterizes his patent as describing how to amplify a eukaryotic gene using a selectable gene (DHFR) and a selection methodology (exposure to methotrexate).[21] Dr. Axel clearly explains in his declaration that he viewed the combined teachings of Axel and the Cabilly specification as being sufficient to enable a person skilled in the art to produce antibodies and antibody fragments in CHO cells without undue experimentation.[22] Dr. Axel did not credit the Axel disclosure, standing alone, as being sufficient to enable production of antibodies or antibody fragments, or as suggesting co-expression of heavy and light chains in one transformed host cell.

In fact, the Office during examination of a related Axel patent application, reached a similar conclusion. In particular, during examination of Application Serial No. 08/395,520, the Office imposed a rejection under 35 U.S.C. § 112, first paragraph, based on its determination that

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[20] Claim 23 of Axel is directed to a process for producing "interferon protein, insulin, growth hormone, clotting factor, viral antigen or antibody." In connection with their amendment, the Axel applicants represented to the Office that:

> [a]s so amended, claim 35 [patent claim 22] and 71 [patent claim 51] and the claims dependent thereon, 36-37 [patent claims 23-24] and 72-73 [patent claims 52-53], respectively, do not require that the protein which is produced be encoded by DNA I. Thus, claims 35-37 [22-24] and 71-73 [51-53] as amended cover production and recovery of thymidine kinase which, as the Examiner acknowledged in the Official Action, is disclosed.

Axel June 7, 1982 Reply at 6.

[21] A copy of the declaration, mailroom date October 5, 1999, was made of record in the reexamination proceeding as an attachment to the February 2007 Office Action.

[22] The Office also refers to the declaration by Dr. Richard Axel, at page 32 of the Final Action.

the Axel disclosure (i.e., standing alone) did not enable production of antibodies in a single transformed host cell. As the Office stated:

> The [Axel] specification does not disclose how to amplify antibody genes. The cloning of functional recombinant antibodies had not occurred at the time the claimed [invention] was made. The production of recombinant antibodies was a milestone in molecular biology requiring teachings not disclosed in the instant specification.

March 20, 1997 Office Action in Application Serial No. 08/395,520 at 6.

(c) Production of Heavy and Light Chains in One Host Cell is Not Required by Axel

At page 28, the Office states that an "antibody" is a "patented embodiment" and observes that the "Axel patent claims are presumed valid under 35 U.S.C. § 282 unless invalidated by 'clear and convincing evidence' and additionally references are presumed to be operable and enabled."[23] The Office reaches this conclusion by first reading Axel as teaching "cotransformation **to generate functional proteins**."[24] Final Action at 30 (emphasis original). Then, it concludes "it is clear that *Axel*'s claims directed to coexpression in a single eukaryotic host cell of proteinaceous materials, which include an antibody ... is referring to the plain meaning of the term 'antibody' as representing a 'functional' antibody-binding immunoglobulin molecule containing at least the variable portions of the heavy and light chain." Id. at 30. It also concludes that Axel "suggests expressing immunoglobulin chains in a single eukaryotic host cell, since *Axel* discloses and claims encoding an antibody that necessarily possesses both light and heavy immunoglobulin chains." Finally, at pages 46-47, the Office refers to evidence of licensing of the Axel patent, reported in a law review article, to assert that the industry recognized that Axel was describing and enabling production of "functional proteins, including antibodies." Final Action at 46.

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[23] The Office's reliance on the presumption of validity of a patent claims to support its interpretation of the Axel disclosure is misplaced. The presumption of validity is a procedural device allocating a burden of proof, and cannot be used to shield scientifically incorrect statements. See, e.g. Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1359-1360, 82 U.S.P.Q.2d 1321, 1329 (Fed. Cir. 2007) (discussing procedural impact of presumption of validity).

[24] As noted above, Axel does not describe production of functional "DNA I" polypeptides. See, e.g., supra at §II(C)(1).

To be clear, Owners' objection to the Office's use of Axel in the rejection is not based on the grounds that the Axel patent claims are invalid. Instead, it is that nothing in Axel suggests (much less requires) that a person of ordinary skill wanting to produce an "antibody" using its procedures would do so by producing heavy and light chains together in one transformed host cell. As Dr. McKnight explains:

> Instead, that person would have understood that the way to approach producing an antibody (or any other multimeric protein) using the Axel methodology would have been to produce only one antibody polypeptide at a time using a host cell co-transformed with a marker gene and a DNA I sequence encoding the desired antibody polypeptide (*i.e.*, produce one co-transformed host cell with a DNA I encoding the antibody heavy chain, and a different co-transformed host cell with a DNA I encoding the antibody light chain). If each chain were successfully produced and isolated from the separate host cell cultures, then the next step would have been to try to combine the chains in a test tube to form the immunoglobulin tetramer or binding fragment. This is the only approach that is consistent with the DNA I + DNA II scheme outlined in the Axel patent, and with the recommendations in the Moore and Kaplan references.

McKnight 2nd Dec. ¶ 27. This approach of producing each antibody chain in separate host cells, followed by combining the chains in a test tube, is the only way of implementing the Axel method in a manner consistent with the procedures described in Axel that call for co-transformation of a host cell with just two DNAs – one encoding a single polypeptide of interest (DNA I) and one encoding a selectable marker protein (DNA II). McKnight 2nd Dec. ¶¶ 21-23, 26-27.

A person of ordinary skill in the art would not have read the term "antibody" as it is used in the Axel claims as meaning an "intact (assembled)" antibody. See Final Action at 12. Several points show that reading is neither necessary nor supported by the Axel disclosure. The Axel claims 7, 23, 29, 37, and 60 are each dependent upon a parent claim that defines the recited antibody as a "proteinaceous material." A "proteinaceous material" is defined at col. 4, lns. 28-29 of Axel as being a "biopolymer formed from amino acids." As Dr. McKnight explains, a "biopolymer" is a single polypeptide consisting of a sequence of amino acid residues linked by peptide bonds, not a multimeric protein complex made up of different polypeptides associated through non-covalent interactions or disulfide bonds. McKnight 2nd Dec. FN 12. Moreover, applying the technique described in Axel for obtaining DNA I sequences to immunoglobulins will produce a DNA I sequence that encodes only a heavy or a light immunoglobulin

polypeptide, not both. As Dr. McKnight explains, using the Axel procedure of using restriction endonuclease digestion of chromosomal DNA will produce DNA I sequences that encode only one antibody polypeptide because the immunoglobulin light and heavy genes are located on different chromosomes. McKnight 2nd Dec. ¶26. In addition, as Dr. McKnight explains, producing only one antibody polypeptide at a time in a transformed cell is the only procedure consistent with the DNA I + DNA II scheme outlined in the Axel patent. See, e.g. McKnight 2nd Dec. ¶24.

Thus, read in the context of the Axel disclosure as a whole, the Axel patent claims clearly require production of only an individual antibody polypeptide, not an assembled (intact) antibody tetramer. Indeed, this interpretation is supported by the fact that there is no discussion anywhere in Axel about producing "intact (assembled) antibodies" in a single co-transformed host cell.[25]

Regardless of whether the Office reads the "antibody" references in the Axel claims as meaning an "intact(assembled)" antibody or as meaning an individual "antibody polypeptide," the presumption of validity of these Axel claims need not be implicated. First, the Office can construe the Axel claims as being directed to production of a tetrameric antibody, but can recognize that one can make this antibody using heavy and light antibody polypeptides individually produced in separate host cell cultures. Alternatively, the Office can read the term "antibody" to mean an antibody polypeptide. Indeed, the only interpretation of the Axel claims that must be ruled out by operation of the presumption of validity is one requiring production of an intact (assembled) antibody by co-expression of heavy and light chains in a single transformed host cell. This is because this interpretation of the Axel antibody claims would render them invalid under 35 U.S.C. § 112, first paragraph, in view of the clear and convincing evidence of record provided by Owners. See, e.g., Phillips v. AWH Corp., 415 F.3d 1303, 1327 (Fed. Cir. 2005) (en banc) (observing maxim that court should resolve ambiguities it perceives to exist in a claim in a manner that would support validity).

The Office's interpretation of the significance of licensing of the Axel patent is also misplaced. As Dr. Walton explains in his declaration under 37 CFR § 1.132, evidence from

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[25] Harris 2nd Dec. ¶¶ 38-40, 44, 48; McKnight 1st Dec. ¶¶ 69-71, 74; Botchan Dec. ¶¶ 50-51, 53.

licensing of the Axel patent, as reported in a law review article, does not support the Office's conclusion that one of ordinary skill in the art would have interpreted the Axel patent claims as being directed to production of functional proteins, including antibodies. Walton Dec. ¶¶ 10, 16. Instead, he explains the more plausible interpretation of this licensing evidence is that the industry recognized Axel as being directed to a technique of using a selectable marker in mammalian host cells allowing for identification of successful transformants from non-transformants. Walton Dec. ¶ 17.

Accordingly, production of an antibody by expression of heavy and light chain genes in a single co-transformed cell is not a patented Axel embodiment, nor is it specifically suggested by Axel.

(d) Rice, Ochi and Oi Reinforce Unpredictability Shown in Axel

The unpredictability shown in Axel in achieving successful transformation and expression of foreign DNA sequences encoding eukaryotic proteins is also shown by the three papers cited by the Office that describe experiments where a lymphoid cell was transformed with a single foreign immunoglobulin light chain gene (i.e., Rice, Ochi and Oi). See McKnight 2nd Dec. ¶¶ 30-37. Dr. McKnight refers to Ochi to illustrate this point, because Ochi shows significant unpredictability even in the simplest experimental model shown by these publications (i.e., restoring expression of a light chain gene in a mutant hybridoma cell line that had lost this capability). See McKnight 2nd Dec. ¶ 31 (discussing Ochi transforming the mutant hybridoma with a single light chain gene isolated from its parental hybridoma line).

Dr. McKnight concludes that Ochi, like Rice and Oi, does not describe or suggest procedures for achieving successful transformation and expression of multiple foreign immunoglobulin genes in a single host cell. He points out Ochi reports significant unpredictability in achieving successful expression of even one foreign light chain gene in a B-cell, despite observing successful transformation of that B-cell line with the foreign gene.[26] See

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[26] As Drs. Harris, McKnight and Rice explain, Rice and Oi also report significant amounts of unpredictability in their respective experiments. See Rice 1st Dec. ¶ 14 ("[M]y experience was that using the same transfection and selection conditions described in the *PNAS* paper with other cell lines or other Ig genes did not routinely yield stable transformants containing even a single exogenous Ig gene."); see also Harris 1st Dec. ¶ 35; Harris 2nd Dec. ¶ 63. Oi describes widely varying degrees of success in transforming and expressing an exogenous light chain gene in various types of lymphoid cells. In particular, Oi reports that some cells could not be

McKnight 2nd Dec. ¶¶ 32-34. In particular, he explains that Ochi reports that 14 cell lines were successfully transformed to incorporate one foreign light chain gene, but only one of these 14 lines showed production of an antibody at levels comparable to the native parental line. See McKnight 2nd Dec. ¶ 32. He further explains that Ochi reports that most of these successfully transformed lines produced little or no light chain protein, and showed no or only trace levels of expression of the light chain gene. See id. at ¶ 33, n.24.

Dr. McKnight concludes:

> Each of these papers [Axel, Rice, Ochi, and Oi] shows that successful transformation and expression of even one foreign immunoglobulin gene in a lymphoid host cell could not be reasonably expected in April 1983. I do not believe these references can be read as suggesting that something even more challenging – expressing two different foreign immunoglobulin genes in one transformed cell would have been something that could be predictably achieved at that time.

McKnight 2nd Dec. ¶ 34. In other words, each of these references (i) reports much simpler experiments than what is required by the '415 patent claims, and (ii) reports significant uncertainty in achieving success in these much simpler experiments. Rice, Ochi, and Oi simply would not have led a person of ordinary skill in the art in April 1983 to conclude that successful transformation and expression of different DNA sequences encoding heavy and light chains in a single transformed host cell based could be predictably achieved. Thus, Rice, Ochi, and Oi, in conjunction with the other cited references, do not suggest modifying the '567 patent claims to yield what is required by the '415 patent claims.

3. The Cited References Teach Away from Producing Two Immunoglobulin Polypeptides in One Transformed Host Cell

The Office has emphasized repeatedly the importance of considering the collective teachings of the cited references. Owners agree, and submit that the collective teachings of the references cited by the Office clearly direct the person of ordinary skill in the art, in April 1983, to attempt production and recovery of only one immunoglobulin polypeptide at a time in a transformed host cell, not two.

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transformed, some cells were transformed but did not express the introduced gene, and others expressed the introduced light chain gene at widely varying levels. See, e.g., McKnight 1st Dec. ¶¶ 109-110; Rice 2nd Dec. ¶¶ 22-25.

In April 1983, the cited references would have led a person of ordinary skill in the art to not pursue the path taken by the '415 inventors of producing both heavy and light immunoglobulin chain polypeptides together in a single transformed host cell. The references that outline plans for producing an immunoglobulin expressly teach producing only one immunoglobulin polypeptide at a time in a host cell. Each reference reporting experimental results shows that expression of even one foreign gene encoding a desired immunoglobulin polypeptide involved considerable unpredictability. None of these references can be read as suggesting – expressly or by implication – expression of two desired immunoglobulin polypeptides in one cell. Thus, Axel, Ochi, Oi, Rice, Kaplan, and Moore considered in combination clearly teach away from the idea of producing heavy and light immunoglobulin polypeptides in a single transformed host cell.

(a) The Prevailing Mindset in April 1983 Was Production of One Eukaryotic Polypeptide at a Time in a Transformed Host Cell

As Dr. McKnight explains, production and recovery of only one desired polypeptide at a time in a host cell was the prevailing mindset in April 1983. See McKnight 2nd Dec. ¶¶ 8-16. He explains he was not aware of any published reports in the scientific literature before April 1983 that even suggested the concept of producing and recovering two different eukaryotic proteins in a single transformed host cell. See id. at ¶ 5. He notes that that every example reported in the Harris review article[27] – which attempts to list every published report of production of a eukaryotic polypeptide in E. coli by 1983 – shows production of only one polypeptide at a time in a bacterial host cell. See id. at ¶ 9.

Dr. McKnight illustrates this mindset by discussing insulin, the only multimeric protein that was produced using recombinant DNA techniques by the time of the invention. See id. at ¶¶ 10-11. Insulin is a relatively simple multimeric protein consisting of two short polypeptide chains. See id. at ¶ 10. Dr. McKnight explains that the two approaches for producing insulin described as of April 1983 each produced only one insulin polypeptide at a time in a transformed host cell. See id.. In each approach, the insulin multimer was assembled in a test tube. See id. at ¶ 11. Dr. McKnight considers this example significant in part because insulin is a far smaller and less complicated multimeric protein than an immunoglobulin molecule. See id. at ¶ 10. A

person of ordinary skill would not have approached production of a much more complicated multimeric protein (e.g., an immunoglobulin molecule) using a more complicated procedure (e.g., production of both chains of an antibody in a single host cell).

(b) Moore and Kaplan Expressly Call for Production of Only One Heavy or Light Chain at a Time in a Transformed Host Cell

Moore and Kaplan perhaps provide the clearest insight into how a person of ordinary skill in the art might have approached production of an immunoglobulin molecule or fragment in April 1983 using recombinant DNA techniques. Each patent describes a prophetic plan for producing an immunoglobulin molecule or fragment using recombinant DNA techniques. And each plan expressly calls for production of heavy and light immunoglobulin polypeptides in separate host cells, and proposes assembly of the multimeric immunoglobulin complex by combining the individually produced chains in a test tube. See McKnight 2nd Dec. ¶¶ 12-13.

The Moore patent describes a plan for producing so-called "rFv" binding molecules. According to Moore, an rFv is made up of short polypeptides that correspond to portions of the variable regions of heavy and light immunoglobulin chains. As the Office acknowledges, the approach taught by Moore for producing an rFv is to produce each of the heavy and light chain components of the rFv binding proteins in separate host cells. See Final Action at 5. After that is done, Moore directs the person of skill to isolate, purify and combine the individual chain preparations in vitro to form the rFv. See McKnight 2nd Dec. ¶ 12; see also Botchan Dec. ¶¶ 11-14, 20-27, 32; McKnight 1st Dec. ¶¶ 19-22; Altman Dec. ¶¶ 11-12; Scott Dec. ¶¶ 8-12.

Kaplan similarly provides a prophetic "roadmap" for producing an immunoglobulin molecule using recombinant DNA techniques that plainly calls for production of only one immunoglobulin polypeptide at a time in a transformed host cell. See McKnight 2nd Dec. ¶ 13; see also Botchan Dec. ¶¶ 74-77; McKnight 1st Dec. ¶¶ 93-96; Harris 1st Dec. ¶ 41; Harris 2nd Dec. ¶¶ 68-70. The Kaplan plan then suggests combining the individually produced chains in a test tube under mildly oxidizing conditions to produce the immunoglobulin tetramer. See McKnight 1st Dec. ¶95; McKnight 2nd Dec. ¶ 13.

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[27] Harris, Genetic Eng'g 4: 125-85, at 129 (1983).

Indeed, it is particularly telling that neither Moore nor Kaplan even mentions the idea of producing both immunoglobulin polypeptides in a single transformed host cell, even though the desired goal was to produce an "rFv" or immunoglobulin molecule, respectively. What this demonstrates is that neither Moore nor Kaplan suggests producing two different immunoglobulin polypeptides in one host cell was something that could have been predictably achieved based on the general knowledge in the field of recombinant DNA expression at the time of their respective disclosures.

(c) Axel Reinforces the Mindset of Producing Only One Eukaryotic Polypeptide in a Transformed Host cell

Axel clearly teaches production and recovery of only one polypeptide at a time in a transformed host cell under its DNA I + DNA II process. See, e.g., McKnight 2nd Dec. ¶¶ 26-27; McKnight 1st Dec. ¶¶ 65-74; Botchan Dec. ¶¶ 50-62; Harris 2nd Dec. ¶¶ 35-48; Harris 1st Dec. ¶¶ 20-30. This is the only scientifically plausible reading of Axel.

Considering Axel in the specific context of producing an "antibody" does not change this conclusion. For example, Dr. McKnight explains that following the DNA I + DNA II process outlined in Axel to produce an immunoglobulin would lead a person of ordinary skill to produce and use a DNA I sequence that encodes only one immunoglobulin chain (not two). See id. at ¶¶ 19, 26-27. This is because the technique disclosed in Axel for isolating DNA I sequences (i.e., endonuclease restriction digestion of chromosomal DNA) will produce DNA I sequences that can encode only one immunoglobulin chain. See id. at ¶ 27.

Nonetheless, the Office attempts to read the Axel abstract to support the idea of producing and recovering multiple proteins of interest (i.e., proteins encoded by DNA I sequences) from a single transformed host cell. See Final Action at 28-29. This is not only a scientifically implausible reading of Axel, it is inconsistent with the text of the Axel abstract. Three instances occur in the abstract of the plural term "genes." Read literally, the first instance is simply a general recapitulation of the idea of inserting different types of "genes" into eukaryotic "cells." See id. at ¶ 29. The second and third instances are referring to techniques for

getting multiple copies of the same DNA I sequence in the host cell.[28] Axel explains that this can be done by using excess copies of the DNA I sequence relative to the DNA II sequence, or by using gene amplification techniques when the DNA I and DNA II sequences are linked. See, e.g., McKnight 2nd Dec. ¶ 29; Harris 2nd Dec. ¶¶ 45-46; Botchan Dec. ¶ 60; McKnight 1st Dec. ¶ 73. The Office's reading of the Axel abstract and the conclusion that Axel specifically suggests production of "functional antibodies" are not scientifically justified. And, as explained above, Axel does not describe production or recovery of any functional polypeptide encoded by a DNA I sequence.

(d) Rice, Ochi, and Oi Further Reinforce the "One Protein-One Host Cell" Mindset Prevalent in April of 1983

As Dr. McKnight explains, Rice teaches transformation and expression of only a single foreign immunoglobulin light chain gene in a B-cell. See McKnight 2nd ¶ 30; McKnight 1st Dec. ¶¶ 79-91; see also Rice 1st Dec. ¶¶ 9-10, 12-13; Rice 2nd Dec. ¶¶ 28-30; Botchan Dec. ¶¶ 63-72; Harris 1st Dec. ¶¶ 31-39; Harris 2nd Dec. ¶¶ 52-67. He and other experts explain that a person of skill in the art would not have found in Rice any basis for concluding that producing a transformed lymphoid cell that independently expressed two different foreign immunoglobulin genes would have been considered predictable in April 1983. See, e.g., McKnight 2nd Dec. ¶¶ 34-37; Rice 1st Dec. ¶¶ 14-15; Rice 2nd Dec. 13-16, 30-32; McKnight 1st Dec. ¶¶ 79-91; Botchan Dec. ¶¶ 63-72; Harris 1st Dec. ¶¶ 31-39; Harris 2nd Dec. ¶¶ 27-28, 54-67. One of these experts was the co-author of the Rice paper, Dr. Douglas Rice. See Rice 1st Dec. ¶¶ 7-17; Rice 2nd Dec. ¶¶ 17, 27-32. Despite this evidence, the Office maintains that a person of ordinary skill in the art would have read Rice, in conjunction with Axel, Kaplan, and Dallas, as specifically

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[28] Owners also invite the Office to review the original abstract proposed by Axel. This abstract was amended by an Examiner's amendment to delete the paragraph indicating that specific types of DNA I proteins could be produced. In addition, the Examiner's amendment modified original language regarding "genes" in the portion of the abstract that is quoted in the Final Action at 30, as follows: "The invention further relates to processes for inserting into eucaryotic cells a multiplicity of DNA molecules [which includes] including genes coding for desired proteinaceous materials [. The insertion of multiple copies of desired genes is accomplished by] cotransformation with the desired genes and with amplifiable genes for a dominant selectable marker . . ." (brackets indicate text that was to be deleted and underlined text is text that was to be inserted per the Examiner). See '216 patent file history, Reply mailed 5 July 1983.

suggesting (and providing motivation for) production of foreign heavy and foreign light chain polypeptides in a single transformed B-cell. See Final Action at 14.[29]

Dr. McKnight reaches precisely the opposite conclusion. As he explains, a person of ordinary skill in the art would have found that Rice, particularly when read with Axel, Kaplan, Moore, Ochi, and Oi, would have reinforced the "one polypeptide-one host cell" mindset that was prevalent in April 1983. See McKnight 2nd Dec. ¶ 37. He explains that Rice, Ochi, and Oi each attempted expression of only one foreign immunoglobulin light chain gene, and each reported unpredictable results. See, e.g., id. at ¶¶ 30-34. Dr. McKnight concludes that these reports of unpredictable results would have led a person of ordinary skill to pursue a more conservative experimental approach (i.e., produce only one polypeptide at a time in the transformed lymphoid cell). See id. at ¶ 37.

(e) Dallas Would Not Have Altered the "One Protein-One Host Cell" Mindset Established by the Other Cited References

As Dr. McKnight explains in his Second Declaration, Dallas does not answer any of the questions raised by the other cited references about producing and recovering multiple foreign eukaryotic proteins in recombinant host cells in April 1983. See McKnight 2nd Dec. ¶¶ 38-44.

As Dr. McKnight explains, the goal of the Dallas invention – production of a genetically transformed E. coli for use as a whole cell vaccine – was a fundamentally different objective than production and recovery of eukaryotic proteins from transformed host cells. See id. at ¶ 40. He explains that Dallas used E. coli genes that encode simple monomeric E. coli cell surface polypeptides, and that Dallas was not required to (and did not attempt to) isolate or recover the expression products of these E. coli genes. See id. Instead, all that Dallas had to do to achieve success was express the E. coli genes in the transformed E. coli cells. See id.

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[29] The Office appears to base this conclusion on its opinion that "Rice demonstrates the successful expression of both heavy and light chains in a host with subsequent assembly into immunoglobulins." Final Action at 13. Owners have previously shown that a person of ordinary skill in the art would not have equated expression of a foreign light chain gene and an endogenous heavy chain gene, or considered it to be equivalent to expressing two different foreign immunglobulin genes in one transformed lymphoid cell. See, e.g., Rice 1st Dec. ¶ 17; Rice 2nd Dec. ¶¶ 29, 32; Harris 1st Dec. ¶ 36; Harris 2nd Dec. ¶¶ 59, 66, 84, 86; Botchan Dec. ¶¶ 67, 72, 99-100; McKnight 1st Dec. ¶¶ 83, 87, 91; McKnight 2nd Dec. ¶¶ 34, 37.

Dr. McKnight considers the nature of the experiments performed in Dallas important when assessing the significance of Dallas to a person of ordinary skill in the art. See, e.g., id. at ¶¶39-43. In particular, he explains that successful transformation and expression of E. coli genes in an E. coli cell would not be considered equivalent to the challenge of achieving successful independent expression of DNA sequences encoding light and heavy immunoglobulin polypeptides in a single transformed bacterial cell in April 1983. See id. at ¶ 41. He points out that the processes governing incorporation and expression of these inserted E. coli genes are essentially natural processes. See id. He also explains that, from an experimental standpoint, carrying out these processes would not have been viewed as presenting technical challenges comparable to those involved in expressing foreign DNA sequences encoding eukaryotic polypeptides. See id. Further, he explains that a person of ordinary skill would not have expected the transformed E. coli cells to encounter any problems in producing or processing the simple E. coli polypeptides encoded by these E. coli genes. See id. at ¶ 42.

Dr. McKnight concludes that a person of ordinary skill would have seen no benefits to offset the additional unpredictability and complexity of expressing two different immunoglobulin polypeptides in a single bacterial cell. See id. at ¶ 46. For example, he points out that the person of ordinary skill would not have expected a bacterial cell to have any capacity to correctly fold the immunoglobulin chains, or facilitate assembly of the immunoglobulin tetramer. See id. at ¶ 47. As he explains:

> I believe a person of ordinary skill would have simply avoided all these problems and uncertainties by producing the heavy and light immunoglobulin chains in separate bacterial host cell cultures. This is what each of the Moore and Kaplan references recommends doing and what the '567 Cabilly patent claims call for. The Dallas publication would not have altered my conclusions from these other references because it had a very different goal and because it provides no guidance at all about producing and recovering foreign eukaryotic proteins from transformed host cells.

Id. at ¶ 48. Dr. McKnight also explains that Dallas provides no guidance about expressing foreign DNA sequences in eukaryotic host cells. See id. at ¶ 41; see also Botchan Dec. ¶¶ 78-83; McKnight 1st Dec. ¶¶ 97-102; Rice 2nd Dec. ¶ 41-43; Harris 2nd Dec. ¶¶ 72-78.

The Office also found Dallas to provide only a limited teaching through its disclosure. During examination of the U.S. counterpart of the Dallas PCT reference (eventually issued as

U.S. Patent No. 5,137,721), the Office determined that "the disclosure is enabling only for claims limited in accordance with the disclosure at pages 5-11." Dallas Office Action of June 5, 1984 (Paper No. 11) at 3. In other words, the examiner found support only for use of E. coli host cells and transformation and expression of E. coli genes encoding specific cell surface adhesion and toxoid polypeptides. See, e.g., Dallas October 28, 1982 Office action (Paper No. 4) at 4; Dallas June 5, 1984 Office action (Paper No. 11) at 3-4; Dallas November 17, 1986 Office action (Paper No. 17) at 3. Dallas eventually conceded this point and limited the claims in order "to clarify the nature of the invention in response to the Examiner's suggestion of overbreadth." Dallas emphasized that "[t]he novelty of the invention is the use in a vaccine of whole cell non-pathogenic E. coli." See Dallas February 20, 1987 Reply (Paper No. 18) at 3.

Accordingly, Dallas would not have altered the teachings and suggestions of the other cited references that call for production of only one immunoglobulin polypeptide at a time in a eukaryotic host cell (i.e., Axel, Rice, Ochi, Oi, Kaplan, and Moore). As Dr. McKnight explains, a person of ordinary skill in the art, considering the collective teachings of the cited references in conjunction with Dallas simply would not have concluded that immunoglobulin heavy and light chain polypeptides should be produced in a single host cell. See McKnight 2nd Dec. ¶¶ 38-39.

4. The Cited References and General Knowledge in the Art Would Not Have Made the '415 Invention Reasonably Predictable to a Person of Ordinary Skill in the Art in 1983.

(a) The Cited References that Provide Experimental Results Report Significant Unpredictability

As Dr. McKnight explains, the '567 patent claims require production of only one chimeric immunoglobulin heavy or light chain in a transformed host cell. The '567 patent claims thus reflect the mindset prevalent in April 1983 that one should produce only one eukaryotic polypeptide at a time in a host cell. The Office combines the '567 patent claims with teachings of the cited references to find that the '415 patent claims would have been considered obvious in April 1983.

Owners have addressed the uncertainty reflected in the experimental results reported in Axel, Rice, Ochi, and Oi above. These references – the only ones that report data from experiments attempting to express DNA sequences encoding eukaryotic polypeptides – report

significant unpredictability in achieving successful transformation and expression of even a single immunoglobulin polypeptide. See, e.g., McKnight 2nd Dec. ¶¶ 6-8, 21-23, 30-34, 50. As Dr. McKnight explains:

> Experimental results would have been important to a person of ordinary skill in the art in April 1983 because many of the biological mechanisms that controlled expression of foreign DNA and assembly of proteins were not well understood at that time. As Dr. Harris observed in his article, "it is clear that not all the rules governing the expression of cloned genes have been elaborated and those rules that do exist are still largely empirical."

Id. at ¶ 6 (quoting Harris, Genetic Eng'g 4: 127-85, at 129 (1983)). Even Dallas, which does not concern producing or recovering a eukaryotic polypeptide, shows some unpredictability regarding its experimental results (e.g., it reports a doubly transformed bacterial cell was unstable and reduced expression levels in a plasmid containing two E. coli genes). See id. at ¶ 41, n.27.

Moreover, in April 1983, there were no published reports describing an experiment having complexity comparable to what is required by the '415 patent. See McKnight 2nd Dec. at ¶ 5. At that time, reports in the scientific literature showed recombinant production of relatively simple monomeric eukaryotic proteins. Even insulin, a simple multimeric protein, was produced by making its individual chains in separate cells and assembling them in a test tube. See id. at ¶¶ 10-11. The mindset reflected by these examples illustrates the general beliefs of those working in the field of recombinant DNA expression about the unpredictability of producing eukaryotic polypeptides in recombinant host cells. As Dr. McKnight concludes:

> ... the publications and patents cited in the Final Action would not have led me (or any other person of ordinary skill in the art) in April 1983 to believe that what was required by the '415 patent could be predictably achieved. Each of the cited references discloses something far less complicated than what the '415 patent requires, and those that report results show significant unpredictability in achieving success in these simpler experiments. In addition, none of the references provide any answers to the questions that these references would have raised in the mind of a person of ordinary skill in the art in April 1983 about making an immunoglobulin molecule or fragment by producing the heavy and light chain polypeptides together in one transformed host cell.

McKnight 2nd Dec. ¶ 7.[30] Collectively, the cited references demonstrate that a person of ordinary skill in the art, in April 1983, would not have had a reasonable basis for believing that the entirety of the '415 patented invention could have been predictably achieved by considering the '567 patent claims with the information and guidance found in Axel, Rice, Kaplan, Dallas, Ochi, Oi, Deacon, Valle 1981, and Moore.

(b) The Predictability of Achieving the Entire '415 Patented Invention Must Be Considered

The assessment of predictability of achieving an invention must be based on the predictability of achieving the claimed invention considered as a whole. See General Foods Corp. v. Studiengesellschaft Kohle mbH, 972 F.2d 1272, 1280, 23 U.S.P.Q.2d 1839, 1845 (Fed. Cir. 1992) (holding that the obviousness-type double patenting analysis conducted by the trial court "violate[d] the fundamental rule of claim construction, that what is claimed is what is defined by the claim taken as a whole, every claim limitation . . . being material"); see also W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1548, 220 U.S.P.Q. 303, 309 (Fed. Cir. 1983) ("In determining obviousness . . . [a] court's restriction of a claimed multi-step process to one step constitutes error."); Schenck v. Nortron Corp., 713 F.2d 782, 785, 218 U.S.P.Q. 698, 700 (Fed. Cir. 1983).

The substantial evidence of record in this case shows that a person of ordinary skill would not have equated the predictability of the entire process required by the '415 patent claims with the predictability of achieving immunoglobulin assembly in a fundamentally different experimental context (e.g., a B-cell transformed with only one immunoglobulin gene, or a frog oocyte injected with mRNA fractions isolated from a B-cell). See, e.g., McKnight 2nd Dec. ¶¶ 31, 47; Harris 1st Dec. ¶ 18; Harris 2nd Dec. ¶¶ 26-27, 90-93, 95, 97; Botchan Dec. ¶ 67-68, 86-94; McKnight 1st Dec. ¶¶ 87-88, 105-108; Rice 2nd Dec. ¶¶ 11-15; Colman Dec. ¶¶ 15-19, 25-36. As noted above, the '415 patent claims require more than simply assembling heavy and light immunoglobulin polypeptides into an immunoglobulin molecule or fragment; they first require (i) transformation with the heavy and light chain DNA sequences, and (ii) transcription and

[30] Several other experts have independently reached this conclusion. See, e.g., Botchan Dec. ¶¶ 15, 16, 62, 66, 72, and 97-104; Rice 1st Dec. ¶¶ 14, 16-17; Rice 2nd Dec. ¶¶ 12-17, 22-26, 33, 35-37; Harris 1st Dec. ¶¶ 15-19, 36; Harris 2nd Dec. ¶¶ 18-18, 27-28, 55-59, 63, 75-78.

translation of these sequences to produce the heavy and light chain polypeptides in the single host cell.

As Dr. McKnight explains, a person of ordinary skill in the art would have based their beliefs about the predictability of achieving the entirety of the '415 patented invention on their expectations about successfully achieving each of the steps required by the claims (i.e., transformation of the cell with two different DNA sequences, correct transcription of both introduced DNA sequences, successful translation of mRNA produced from transcription of each sequence), not just assembly of the immunoglobulin molecule or fragment. See, e.g., McKnight 2nd Dec. ¶¶ 4, 7-8.

That person's expectations about achieving all these steps would have been influenced by what was known in April 1983 about natural B-cells. At that time, it was widely believed that B-cells had unique capabilities and properties that enabled them to properly produce heavy and light chain polypeptides, process the polypeptides, and assemble the processed polypeptides into an immunoglobulin molecule. See id. at ¶¶ 31, 47; see also Harris 1st Dec. ¶ 18; Harris 2nd Dec. ¶¶ 26-27; Botchan ¶¶ 67-68; McKnight 1st Dec. ¶¶ 87-88; Rice 2nd Dec. ¶¶ 11-15. These capabilities were believed to depend on many different factors, as is illustrated by the scientific literature which shows that the proper functioning of the B-cell could be disrupted by "incorrect" or unbalanced expression of both of the endogenous immunoglobulin genes, the state of development or differentiation of the B-cell, the presence of the amounts of heavy and light chain proteins in the B-cell, and the presence of possible B-cell specific "chaperone" proteins such as BiP, and other factors. See, e.g., Harris 2nd Dec. ¶¶ 25-28, 63; McKnight 1st Dec. ¶¶ 87-90; Botchan Dec. ¶¶ 67-68; Rice 2nd Dec. ¶¶ 11-16.

The papers describing experiments where an exogenous immunoglobulin light chain gene was used to genetically transform a lymphoid cell show that these types of genetic changes to lymphoid cells had unpredictable consequences. These included, in particular, consequences that affected the stability of the cells and their ability of preserve their native functions. Extensive evidence has been provided in this proceeding on these points. See, e.g., McKnight 2nd Dec. ¶¶ 6-7; McKnight 1st Dec. ¶¶ 83, 85-86, 88, 104; Harris 2nd Dec. ¶¶ 23-28; Botchan Dec. ¶¶ 67-68, 71; Rice 2nd Dec. ¶¶ 11-16.

These observations have two consequences in the present case. First, the present record shows that a person of ordinary skill in the art would have had significant reasons to doubt that one could successfully practice the claimed invention even in a B-cell. One would need to transform the B-cell with two different foreign immunoglobulin genes and achieve "successful" expression of both genes, all without affecting the viability of the cell, or disrupting the processes (which were not understood at the time) that regulated expression of immunoglobulin genes, production and folding of the different immunoglobulin polypeptides, and assembly and secretion of the antibody tetramer. See, e.g., Harris 1st Dec. ¶ 18; Harris 2nd Dec. ¶¶ 25-28, 54-67; Botchan Dec. ¶¶ 67-68; McKnight 1st Dec. ¶¶ 87-88; Rice 2nd Dec. ¶¶ 11-16.

The Office has dismissed this evidence by arguing that "successful lymphocyte immunoglobulin H and L chain expression and secretion of functional antibody is the norm." Final Action at 36. While these events might be "expected" to occur in a native unmodified B-cell, the Office identifies no basis for asserting that a person of ordinary skill in the art would "expect" these events to occur in a recombinant, genetically modified lymphoid cell. Given the showings of lack of expression or of variable levels of expression of a single immunoglobulin gene in Rice, Ochi, and Oi, the person of skill would not have expected that the same conditions present in a normal unmodified B-cell could be predictably reproduced in a B-cell transformed with heavy and light chain DNA sequences. Therefore, the evidence regarding heavy chain toxicity, unbalanced expression, chaperone proteins, etc., must be considered in the context of evaluating the question of whether a person of ordinary skill could have predictably achieved the '415 patented invention using the teachings of the cited references.

Second, this knowledge about native B-cell functions would also have led the person of ordinary skill in the art to believe that expression of DNA sequences encoding heavy and light chain polypeptides in host cells other than B-cells would entail significant unpredictability and formidable practical challenges. For example, the experiments described in Axel failed to result in expression of even a single DNA I sequence. Expression of DNA sequences encoding two immunoglobulin polypeptides in bacterial cell lines would be even further afield, and the complexities and uncertainties associated with producing and recovering two different immunoglobulin proteins from such host cells would have been considered significant.

Finally, Owners observe that testimony of qualified experts under 37 C.F.R. § 1.132 is evidence that must be considered and given weight by the Office, and that the Office has not cited contrary evidence to respond this evidence. See In re Zeidler, 682 F.2d 961, 967, 215 U.S.P.Q. 490, 494 (C.C.P.A. 1982) (Board committed reversible error in "substitut[ing] its judgment for that of an established expert in the art" to assess obviousness); In re Katzschmann, 347 F.2d 620, 622, 146 U.S.P.Q. 66, 68 (C.C.P.A. 1965) ("We do not think it was the intent of section 103 that either the examiner, the board or this court should substitute their own speculations for the factual knowledge of those skilled in the art."); In re Fay, 347 F.2d 597, 603, 146 U.S.P.Q. 47, 51 (C.C.P.A. 1965); M.P.E.P. § 716.01 et seq.

(c) A Hypothetical Doubly-Transformed B-Cell Cannot Establish Reasonable Expectations Relevant to the '415 Claims

The Office asserts that "in light of the Rice and Baltimore teaching, it would be reasonable for one of ordinary skill in the art to expect that expressing a light and heavy chain of the same antigen specificity in a competent host would result in the assembly of a functional antibody." Final Action at 33. The Office makes similar conclusions regarding the teachings of Ochi and Oi. See Final Action at 38 ("*Ochi* and/or *Oi* reference provide additional motivation to co-transform a single mammalian cell with appropriate light and heavy antibody chains with a reasonable expectation of producing secreted, assembled and functional antibody.").

The Office's conclusions from Rice (i.e., that it "demonstrates the successful expression of both heavy and light chains in a host with subsequent assembly into immunoglobulins") are inconsistent with the evidence of record. See Final Action at 13. As various experts have explained, Rice would not have set expectations about expression of two foreign immunoglobulin genes based on its experimental results. See, e.g., Rice 1st Dec. ¶ 12; Rice 2nd Dec. ¶¶ 27-28, 32; McKnight 1st Dec. ¶ 81. Specifically, a person of ordinary skill in the art would not have interpreted the observation in Rice that there was continued expression of the cell's endogenous (native) heavy chain gene as equivalent to, much less a "demonstration" of, successful expression of a foreign recombinant heavy chain gene. See, e.g., Rice 1st Dec. ¶¶ 11, 16; Rice 2nd Dec. ¶ 27. This observation fails to appreciate the evidence of record explaining that a person of ordinary skill in the art would not have read Rice as suggesting that one should extend its teachings to achieve successful expression of two different foreign immunoglobulin

genes in one transformed B-cell. See, e.g., Rice 1st Dec. ¶¶ 12-17; Rice 2nd Dec. ¶¶ 23-32; Harris 2nd Dec. ¶¶ 57-62; McKnight 1st Dec. ¶¶ 81-83, 87, 91. The Office has offered no contrary evidence on this point.

The only evidence identified by the Office supporting its assertions is the third party declaration of Dr. David Baltimore. In paragraph 5 of his declaration, Dr. Baltimore observes that "I and other [sic] working in the field would have expected that if two chains were expressed, they would form a functional antibody."

First, Dr. Baltimore does not suggest that he or a person of ordinary skill would have found production of a mammalian cell that successfully expressed two different foreign immunoglobulin genes predictable in April 1983. Second, as Dr. McKnight points out, Dr. Baltimore "does not say that a person of ordinary skill would have been motivated by his paper or anything else in the literature at the time of the invention to try to produce an immunoglobulin by independently expressing foreign heavy and foreign light chain genes in a single transformed cell." McKnight 2nd Dec. ¶ 35. Finally, Dr. Baltimore carefully limits his conclusions to a hypothetical situation not discussed or even mentioned in Rice.[31] As Dr. McKnight points out, whether such a hypothetical cell could have been made or would successfully express two foreign immunoglobulin genes would have been a critical "if" in the mind of the person of ordinary skill in the art assessing the predictability of the '415 patented inventions. See McKnight 1st Dec. ¶¶ 89-90; McKnight 2nd Dec. ¶ 35.

Dr. Baltimore also presents only his personal opinions, which cannot be regarded as the beliefs and expectations of a person of ordinary skill in the art. By April 1983, Dr. Baltimore had skills, training and experience far beyond those that would have been possessed by a person of ordinary skill. See Rice 2nd Dec. ¶¶46-48; see also May 2007 Response at 41-42. These extraordinary skills would have given him unique insights, perspectives and beliefs that would not have been shared by the person of ordinary skill. Despite this, the Office asserts that Dr. Baltimore qualifies as one of ordinary skill in the art because he has "at least" the level of

education and experience that the owners acknowledged to be ordinary skill. See February 2008 Office Action at 35.

Owners submit this standard is inconsistent with prevailing law. As the Federal Circuit explained in Envt'l Designs, Ltd. v. Union Oil Co. of Cal., 713 F.2d 693, 218 U.S.P.Q. 865 (Fed. Cir. 1983), someone with skills far above and beyond those of ordinary skill in the art cannot be considered one of ordinary skill in the art:

> The important consideration lies in the need to adhere to the statute, *i.e.*, to hold that an invention would or would not have been obvious, as a whole, when it was made, to a person of "ordinary skill in the art"-not to the judge, or to a layman, or to those skilled in remote arts, or to geniuses in the art at hand.

713 F.2d at 697, 218 U.S.P.Q. at 868. (emphasis added) See also Hybritech Inc. v. Abbott Labs., 4 U.S.P.Q.2d 1001, 1008-1009 (C.D. Cal. 1987) (finding that "persons of superior skill, intellect and insight" who "were leading authorities" in the field did not qualify as persons of ordinary skill in the art); Studiengesellschaft Kohle mbH v. Dart Indus., Inc., 549 F.Supp. 716, 732, 216 U.S.P.Q. 381, 391 (D. Del. 1982) (holding that Nobel laureate's theorizing did not represent the application of "ordinary skill in the art of which said subject matter pertains").

Dr. Baltimore's opinions, as expressed in his declaration, neither (i) contradict Owners' assertions regarding the predictability of achieving the claimed invention of the '415 patent, taking into account all of the limitations of the claims, nor (ii) constitutes appropriate evidence of the views and expectations of a person of ordinary skill in the art in April 1983. As such, Dr. Baltimore's opinions are plainly outweighed by the evidence provided by patentee. See In re Brandstadter, 484, F. 2d 1395, 1405-1407, 179 U.S.P.Q. 286, 293-295 (C.C.P.A. 1973) (indicating that an affidavit or declaration may have little weight when considered in light of all of the evidence of record in the application).

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[31] This also demonstrates that Dr. Baltimore's opinion does not concern what is actually described in Rice, but is instead an opinion about a hypothetical experiment, employing an equally hypothetical B-cell, that was never performed in the time frame of the invention. The Office has not contested this point. As a result, the Baltimore declaration cannot be properly considered in this proceeding because it is not expressing any opinion that "explain[s] . . . printed publications in more detail." See M.P.E.P. § 2258(I)(E).

(d) The Xenopus Oocyte Microinjection Experiments Do Not Establish that the '415 Claimed Invention Could Have Been Predictably Achieved in April 1983

The extensive evidence of record demonstrates that a person of ordinary skill in the art in early April 1983 would have appreciated that the experimental results produced by microinjecting mRNA fractions into of frog (Xenopus) oocytes would have no relevance to the predictability of transforming and expressing foreign DNA sequences in a genetically transformed host cell. See, e.g., Colman Dec. ¶¶ 21-24; Botchan Dec. ¶¶ 86-94; McKnight 1st Dec. ¶¶ 105, 107-108. Dr. McKnight provides further factual evidence that supports a conclusion that a "person of ordinary skill would have viewed the differences between using vector DNA and microinjection of mRNA fractions as being substantive and significant in April 1983." See McKnight 2nd Dec. ¶¶ 49-54.

As Dr. McKnight explains, the experiments reported in Valle 1981 and Deacon used impure mRNA extracts from B-cells that had successfully transcribed their immunoglobulin genes. See id. at ¶ 52. He points out that this meant that RNA transcripts other than those encoding the heavy and light immunoglobulin polypeptides were injected into the oocytes. Id. He explains that a person of ordinary skill in the art would have expected that translation of these other mRNA transcripts would have produced proteins that likely would have contributed to the successful translation and assembly of the immunoglobulin in the oocyte. See id. For example, he explains that such person would have assumed that the mRNA fractions would likely have included mRNA transcripts encoding the as-then not understood BiP protein, which was believed to play a role in immunoglobulin polypeptide folding and immunoglobulin tetramer assembly in B-cells. See id. (referring, e.g., to Valle 1981 at 339, col. 2).

Dr. McKnight concludes that the oocyte experiments would have provided no guidance to the person of ordinary skill about achieving successful transformation of cells and successful transcription of foreign DNA sequences in a transformed host cell. See id. at ¶¶ 49-54. He explains that by using mRNA fractions isolated from a B-cell that was successfully expressing its endogenous immunoglobulin genes, this simply avoids the critical step of achieving successful expression of foreign DNA sequences that have been used to transform a host cell. It also sidesteps issues of producing correct mRNA transcripts from the inserted DNA (a problem

reported in Axel), and proper timing and levels of expression of immunoglobulin genes within a transformed host cell.[32] See, e.g., May 2007 Response at 69 (citing Botchan Dec. ¶¶ 88-89; and Ross, Microb. Rev. 59(3): 423-450 (1995)). For these reasons, Dr. McKnight concludes that Deacon and Valle 1981 would not have influenced the reasonable expectations of the person of ordinary skill in the art in April 1983 about achieving the '415 patent claims. See McKnight 2nd Dec. ¶ 49.

The Office again cites statements made in the European Patent Office opposition proceedings. See Final Action at 42-45. The Office's reliance on the statement as an admission is improper because it is not an admission as to a fact, but mere attorney argument made in a foreign proceeding in relation to another party's patent. See May 2007 Response at 71-73. Moreover, the target of this statement – the EPO Board conducting the opposition proceeding – did not rely on this in any manner in its decision. Owners have also explained that even if this attorney argument were to be considered an admission by one of the Owners, the M.P.E.P. prohibits use of such an admission, because it was submitted by a third party in this ex parte reexamination proceedings.[33] Most importantly, however, the evidence of record establishes that these statements are irrelevant because they are scientifically incorrect. See, e.g., McKnight 1st Dec. ¶¶ 106-108; Botchan Dec. ¶¶ 90-91; Harris 2nd Dec. ¶ 95; Colman Dec. ¶ 15; McKnight 2nd Dec. ¶ 51. Owners submit that the testimony of qualified scientists who can accurately convey the opinions of a person of ordinary skill in the art at the time of the invention, especially

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[32] In addition, a person of ordinary skill in the art would not have characterized a microinjected Xenopus oocyte as a transformed host cell within the scope of the '415 patent claims. See, e.g., McKnight 2nd Dec. ¶ 53; Colman Dec. ¶¶ 15, 17-25; McKnight 1st Dec. ¶¶ 105, 107-108; Botchan Dec. ¶¶ 85-86, 89-92. Successfully transformed host cells must pass the foreign DNA onto their progeny -- but Xenopus oocytes do not produce progeny. As Dr. Colman also explained, "[b]ecause an oocyte cannot replicate, it cannot function as a host cell as I understand the meaning of that term from the '415 patent." Colman Dec. ¶ 19.

when based on their personal experiences, should be given more weight and deference than attorney argument provided in a foreign jurisdiction regarding another party's patent. Cf. In re Fay, 347 F.2d 597, 603-604, 146 U.S.P.Q. 47, 51-52 (C.C.P.A. 1965).

D. Strong Evidence of Secondary Considerations Supports the Conclusion that the '415 Patent Claims Are Not Obvious

As noted above, among the factors that must be evaluated in considering obviousness-type double patenting are objective indicia of nonobviousness, also referred to as secondary considerations. See M.P.E.P. § 804(II)(B)(1). See also KSR, 127 S.Ct. at 1739, 82 U.S.P.Q.2d at 1395 (directing courts to consider "secondary considerations that would prove instructive" when applying the Graham factors (emphasis added)). Secondary considerations "constitute[] independent evidence of nonobviousness," and "may often be the most probative and cogent evidence of nonobviousness in the record." Ortho-McNeil Pharmaceutical, Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1365, 86 U.S.P.Q.2d 1196, 1202 (Fed. Cir. 2008) (citing Catalina Lighting, Inc. v. Lamps Plus, Inc., 295 F.3d 1277, 1288, 63 U.S.P.Q.2d 1545 (Fed. Cir. 2002)).

Particularly relevant secondary considerations are licensing practices showing industry respect/acquiescence and evidence of commercial success. See WMS Gaming Inc. v. Int'l Game Technology, 184 F.3d 1339, 1360, 51 U.S.P.Q.2d 1385, 1400 (Fed. Cir. 2008); Arkie Lures, Inc. v. Gene Larew Tackle, Inc., 119 F.3d 953, 957, 43 U.S.P.Q.2d 1294, 1297 (Fed. Cir. 1997); Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1539, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983). As the Federal Circuit explained in Arkie Lures, successful sales of a patented invention and numerous licenses granted pursuant to the patent "are tributes to ingenuity." 119 F.3d at 957, 43 U.S.P.Q.2d at 1297. There must, of course, be a nexus between the objective evidence of

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[33] See M.P.E.P. § 2258(I)(F). The Office responds that the more relevant guidance on use of admissions submitted by third parties appears in Section 1 of M.P.E.P. § 2258(I)(F), rather than in the section relied upon by owners, i.e., Section 2. See Final Action at 44. Owners respectfully disagree. Section 2, upon which the Owners rely, addresses the use of admissions "[a]fter reexamination has been ordered", and appears under the subheading "Reexamination Ordered, Examination on the Merits." Section 1, on which the Office relies, is not relevant to the question at issue because it addresses use of admissions for purposes of the "Initial Reexamination Determination and Order." In the context of the Final Action, the Office is clearly not using the admission as part of an initial reexamination determination. The Office also cites four cases to support its position, but none of those cases involve admissions submitted by third parties, but rather admissions made by the patent applicant, himself, as part of the application/specification. See Ex parte Seiko Koko Kabushiki Kaisha, 225 U.S.P.Q. 1260, 1262 (Bd. Pat. App. & Inter. 1984); Ex parte Kimbell, 226 U.S.P.Q. 688, 689-690 (Bd. Pat. App. & Inter. 1985); Ex parte McGaughey, 6 U.S.P.Q.2d 1334, 1339 (Bd. Pat. App. & Inter. 1988); In re Nomiya, 509 F.2d 566, 570, 184 U.S.P.Q. 607, 611 (C.C.P.A. 1975).

nonobviousness and the claimed invention at issue. See WMS Gaming Inc., 184 F.3d at 1360, 51 U.S.P.Q.2d at 1400.

Compelling evidence of nonobviousness of the '415 patent claims over the '567 patent claims is present in this case based on its licensing record and commercial success. As explained in the accompanying declaration of Dr. Finton Walton under 37 C.F.R. § 1.132, the '415 patent claims have been extensively licensed throughout the biotechnology and pharmaceutical industries, and enjoy substantial commercial success. Indeed, this is objective evidence that the Supreme Court, Federal Circuit, and district courts have found to be particularly persuasive in the context of evaluating obviousness.

The evidence cited by Dr. Walton shows that licenses have been granted under the '415 patent to at least 35 different companies. See Walton Dec. ¶ 25. Many of these licenses have been granted to large, sophisticated, patent-savvy companies in the biotechnology and pharmaceutical industries. See id. at ¶ 30. Notably, some companies took licenses to only the '415 patent and not the '567 patent while both patents were in force, and some of the Axel licensees also took independent licenses under the '415 patent. See id. at ¶¶ 26-28.

Dr. Walton explains, based on his extensive experience in evaluating license agreements, that this independent licensing reflects a widespread belief in the industry that the '415 patent claims define independently patentable inventions relative to the '567 patent claims, considered with the prior art. See id. at ¶ 40. As Dr. Walton explains, sophisticated companies usually do not usually enter into license agreements with substantial licensing fee obligations without assessing whether (i) their activities would lead to a finding of infringement of the licensed patent, and (ii) the licensed patent is valid. See id. at ¶¶ 9, 38-39. He notes this general principle is particularly true for companies that took licenses under both the '415 and '567 patents. See id. at ¶ 27.

Dr. Walton also provides an analysis of the licensing revenue that has been received from licensees of the '415 patent. Dr. Walton's conservative estimate of licensing revenue that can be attributed exclusively to the '415 patent exceeds $346 million. See id. at ¶¶ 34-37. Dr. Walton concludes that this licensing revenue establishes significant recognition by others, and commercial success attributable to the '415 claims. See id. at ¶¶ 37-46.

Dr. Walton's analysis of the '415 licensing history and revenue provides substantial evidence of industry respect for and acquiescence of the '415 patent. Walton Dec. ¶¶ 37-41. This evidence also demonstrates substantial commercial success of the '415 patented invention, and that this success is independent of the success of the '567 patent claims. See id. at ¶¶ 44-46. Both factors provide compelling secondary indicia of non-obviousness of the '415 patent claims, and do so in particular relevance to the '567 patent claims. Owners submit this evidence of secondary indicia of non-obviousness to reinforce the conclusion that the '415 patent claims are not obvious over the '567 patent claims, considered with the cited references.

E. Status of Dependent Claims

The Office has rejected dependent claims 5-10, 12, 14, 19-20, 22, 26-32 and 34-36. Final Action at 16-20. Each of the rejections is predicated on the Office's determination that claims 1-4, 11, 13, 15-18, 21, 23-25, and 33 are unpatentable for reasons of obviousness-type double patenting. For example, the Office has rejected dependent claims 9 and 29 requiring that the immunoglobulin molecule or fragment to be secreted by the transformed host cell.

As explained above, Owners submit the rejection of claims upon which claims 5-10, 12, 14, 19-20, 22, 26-32 and 34-36 depend is improper and should be withdrawn. Owners further submit that if the rejections of the claims upon which these claims are withdrawn, no basis would exist for imposing rejections of these dependent claims. Owners also note that they have previously provided additional reasons why these claims are not rendered further obvious over the cited references (e.g., showing that there is no discussion or suggestion anywhere in Rice or Axel of secreting immunoglobulin molecules or fragments from a transformed host cell). Nov. 2005 Response at 32-56; Oct. 2006 Response at 27-70; May 2007 Response at 75-80. Accordingly, Owners respectfully request withdrawal of the rejection of dependent claims 5-10, 12, 14, 19-20, 22, 26-32 and 34-36.

III. Conclusion

In view of these remarks, Owners respectfully submit that claims 1-36 of the '415 patent are not unpatentable for reasons of obviousness-type double patenting based on the '567 patent, in view of Axel, Rice and Kaplan, further in view of Dallas, and further in view of Deacon, Valle 1981, or Ochi, alone or further in view of Moore, and optionally further in view of Builder or

Accolla. Owners respectfully submit that all issues raised by the Office and outstanding from the Second Office Action have been fully addressed, and that no grounds exist for refusing to grant Owners a reexamination certificate affirming the patentability of claims 1-36 of the '415 patent.

The Commissioner is hereby authorized to charge Deposit Account No. 18-1260 for any additional fees required in connection with the filing of this Response.

Respectfully submitted,

Date: June 6, 2008

By: _____
Jeffrey P. Kushan, Reg. No. 43,401
SIDLEY AUSTIN LLP

CERTIFICATE OF SERVICE

The undersigned hereby certifies that copies of this paper are being served by first class mail delivery on the date shown below to each of the following:

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SIGNATURE	David L. Fitzgerald, Reg no. 47,347 PRINTED NAME	6/6/08 DATE